Posaconazole for Chronic Refractory Coccidioidal Meningitis

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Coccidioidal meningitis is a potentially lethal infection. Disease progression while taking fluconazole is a common complication and safe, effective, alternative treatments are limited. Posaconazole therapy resulted in symptomatic and laboratory improvement in 2 patients and clinical improvement in a third patient with chronic, previously unresponsive coccidioidal meningitis.

Coccidioides immitis and posadaii are dimorphic fungi commonly found in the southwestern United States. Although the majority of infections are asymptomatic or result in a self-limited respiratory illness, ~0.5% of infections spread beyond the lungs [1]. A severe form of extrapulmonary disease is coccidioidal meningitis, which if untreated is invariably fatal. Most patients receive oral fluconazole, although this is only effective in 70% of cases and disease progression remains a significant problem [1, 2]. We present 3 patients with coccidioidal meningitis and disease progression on high-dose fluconazole. Two were effectively treated with posaconazole, while the third improved clinically with combination amphotericin B and posaconazole. To our knowledge this is the first documented case series of posaconazole for coccidioidal meningitis unresponsive to fluconazole.

Case 1 is a 16-year-old Hispanic male diagnosed with coccidioidal meningitis by a 1:8 Coccidioides complement fixation on the cerebral spinal fluid (CSF) at age 3. Obstructive hydrocephalus necessitated placement of a ventriculoperitoneal shunt (VPS). He was treated with fluconazole 10 mg/kg/day with clinical improvement, although he experienced learning problems and underwent 2 revisions of his VPS due to tube leaks. At 8 years old, he developed a shunt obstruction with associated ventriculitis. His CSF culture grew Coccidioides immitis. His VPS was replaced. The fluconazole dose was increased to 12 mg/kg/day, a regimen that he was generally able to adhere to with occasional periods of missing doses.

Beginning at 13 years of age, he underwent 4 VPS revisions and a third ventriculostomy in an 18-month period. The first surgery revealed a large fungal aggregation obstructing the shunt. CSF cultures were positive for Coccidioides immitis at each procedure. The isolate was tested for susceptibility at the Fungus Testing Laboratory, University of Texas-San Antonio, and had a fluconazole minimum inhibitory concentration (MIC) of 32 µg/mL and a posaconazole MIC of 0.06 µg/mL. While he was hospitalized in the intensive care unit with headache, confusion, and altered mentation, posaconazole 400 mg twice daily was added. His confusion resolved, allowing his return to school. After 7 months of combinationazole therapy, CSF cultures taken after the failure of his third ventriculostomy were negative. Posaconazole levels on the serum and CSF were 0.48 and 0.39 µg/mL respectively, while the fluconazole CSF concentration of 22.8 µg/mL was below the MIC. A subsequent CSF sample obtained 2 weeks later remained negative. Fluconazole was stopped. He has done well for the past year.

Case 2 is a 39-year-old Hispanic male diagnosed with coccidioidal meningitis by CSF culture. He was treated with fluconazole 400 mg daily. Two years later, he developed hydrocephalus and a VPS was placed. Subsequently, he received high-dose fluconazole at 800, then 1200 mg daily, which he took regularly. After a year of treatment, he developed foot drop, left-sided weakness, and papilledema. His symptoms were attributed to cerebral ischemia from progressive CNS coccidioidomycosis. He was started on posaconazole 400 mg twice a day and improved over the next 2 years. He was then incarcerated and during that time received fluconazole therapy. On fluconazole his weakness returned, and he was unable to walk. A cerebral lacunar infarct was found by magnetic resonance imaging (MRI). He required hospitalization and rehabilitation therapy, throughout which he was treated with daily intravenous (IV) liposomal amphotericin B monotherapy. After physical rehabilitation he was placed back on posaconazole therapy. While he has residual weakness and visual defects from the cerebral infarcts, he is otherwise without evidence of disease progression. His serum complement fixation is currently negative at <1:2.

Case 3 is a 23-year-old black male infected with human immunodeficiency virus (HIV) who presented with culture-positive Coccidioides immitis meningitis. He was treated with fluconazole 800 mg daily for over a year with questionable adherence, until he...
acutely developed lethargy and peripheral vision loss. An MRI showed evidence of meningitis and mild hydrocephalus, and the fluconazole was changed to voriconazole 200 mg twice daily. After 4 months he continued to have fatigue, dizziness, ataxia, and generalized weakness. There was continued meningeal enhancement and stable, mild hydrocephalus on MRI, so the voriconazole was changed to IV liposomal amphotericin B 360 mg 3 times a week and posaconazole 400 mg twice daily. After 2 months of combination therapy, the liposomal amphotericin B was stopped, and he continued posaconazole monotherapy. Although his CSF has remained culture positive throughout treatment, after a year of posaconazole he has a normal neurologic examination, improved CSF pleocytosis (Table 1), resolved meningeal enhancement, and improved hydrocephalus on MRI.

Coccidioidal meningitis is a chronic, incurable form of coccidioidal infection. Primary infection results from inhalation of arthroconidia. The pathogenesis of disseminated disease is unclear but thought to be due to endospores within macrophages traveling from the lungs through the lymphatics to the bloodstream [1]. The most common symptom of coccidioidal meningitis is a progressive, unremitting headache, which may be accompanied by altered mentation, personality changes, vomiting, gait abnormalities, and focal neurological deficits. Obstructive hydrocephalus is common, especially in children. Other complications include cerebral infarction, spinal arachnoiditis, and rarely, cerebral abscess. Without treatment, death typically occurs within 2 years of diagnosis.

Oral fluconazole is the standard therapy since the 1993 study by Galgiani et al [2] demonstrated a 79% response rate to treatment. Therapy is life-long, as off-treatment relapses are common and potentially fatal [3]. For patients who are unresponsive to fluconazole, options are limited. Intrathecal amphotericin may be used, and case reports have demonstrated some success with voriconazole [4–6]. The use of posaconazole for coccidioidal meningitis has not been evaluated in humans.

Posaconazole is a newer triazole antifungal that also works by inhibiting the enzyme lanosterol 14a-demethylase blocking the formation of ergosterol, a necessary component in fungal cell membranes [7]. While posaconazole is a CYP3A4 inhibitor, and subject to drug-drug interactions with substrates of this metabolizing enzyme, there is no demonstrable antagonism and possible synergy with other antifungal agents including amphotericin B allowing for the use of combination therapy [8].

The recommended posaconazole adult dose is 800 mg a day in 2–4 divided doses and is only available in an oral suspension to be administered with a high fat meal for improved absorption [7]. Posaconazole is approved for prophylaxis against invasive fungal infections in immunocompromised patients and for treatment of primary and refractory oropharyngeal candidiasis. The large volume of distribution of posaconazole suggests extensive extravascular space and tissue penetration leading to higher tissue levels. This makes it a good candidate for the treatment of central nervous system disease.

There is one previously reported case of posaconazole use for coccidioidal meningitis in a human. A 43-year-old woman with persistently positive CSF cultures and worsening obstructive hydrocephalus, despite 7 years of treatment with fluconazole, demonstrated symptomatic and radiographic improvement after a year of posaconazole therapy [9].

Although information is limited, posaconazole appears to be highly effective in the treatment of chronic nonmeningeal coccidioidomycosis, with a favorable response in 17 (85%) of 20 patients [10]. In a case series of patients with refractory Coccidioides posadaii skin, bone, and/or lung disease, 5 of 6 patients demonstrated symptomatic and serologic improvement with posaconazole [11]. Additionally, in a study of 15 patients with previously unresponsive pulmonary or disseminated coccidioidomycosis, 7 experienced a partial response and 4 responded completely (73% response rate) [9].

Posaconazole is generally well tolerated. The main adverse events reported have been gastrointestinal effects, rash, and elevated transaminases [7, 9]. Our patients tolerated posaconazole well without significant adverse effects.

The relationship between plasma drug concentrations and anticcoccidioidal activity is not clear. In case 1, we demonstrated possible fluconazole resistance based on the high MIC. Catanzaro et al [10] performedazole susceptibility testing data on 12 isolates from patients with chronic nonmeningeal coccidioidomycosis. Decreased susceptibility to fluconazole based on epidemiological cutoff values in wild-type organism was noted with MICs of 12.5–50 μg/mL [10]. Although the posaconazole MICs varied from 0.39 to 3.13 μg/mL, they were able to

Table 1. Cerebral Spinal Fluid Response to Posaconazole

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<thead>
<tr>
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<th>CSF prior to posaconazole</th>
<th>CSF on posaconazole</th>
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<tbody>
<tr>
<td>Case 1</td>
<td>219 78 47 Positive</td>
<td>1 10 62 Negative</td>
</tr>
<tr>
<td>Case 2a</td>
<td>52 52 55 Negative</td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>1020 340 10 Positive</td>
<td>136 158 41 Positive</td>
</tr>
</tbody>
</table>

Abbreviation: CSF, cerebral spinal fluid; WBC, white blood cell count.
*a Please note that patient 2 remains symptom free and CSF on posaconazole therapy has not been obtained.
achieve mean plasma concentrations of 0.203–3.350 μg/mL, typically higher than the MIC [10]. Our case 1 patient had posaconazole plasma concentrations of 0.23–2.5 μg/mL, well above the MIC (0.06 μg/mL) for his organism.

The significance of CSF posaconazole concentrations is unknown. In a rabbit model of cryptococcal meningitis the fungal burdens were significantly decreased despite undetectable levels of drug in the CSF [12]. In case 1, in contrast to the earlier CSF posaconazole concentration above, a subsequent concentration was below the assay limit despite a concurrent serum level of 0.33 μg/mL. He nonetheless maintains a sterile CSF culture, complement fixation, and is clinically stable. These data suggest that posaconazole has variable CNS penetration perhaps related to the degree of meningeal inflammation, and continuously detectable CSF posaconazole is not required for suppression of coccidioidal replication.

Posaconazole is a potent antifungal agent with few adverse effects. In our series of 3 patients, all of whom failed fluconazole therapy and 1 of whom also failed voriconazole, we were able to demonstrate symptomatic improvement in all patients and negative CSF cultures and serum complement fixation in 2 patients. Given our clinical success, posaconazole may be considered for the treatment of refractory coccidioidal meningitis.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**